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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Application Number: 10/588,458
Filing Date: August 04, 2006
Appellant(s): MATHEUS ET AL.

Anthony J. Zelano
For Appellant

SUPPLEMENTAL EXAMINER'S ANSWER

This is in response to the Reply Brief filed 1/19/2010 appealing from the Office action mailed 11/19/2009.

Responsive to the Reply Brief filed on 1/19/10, a supplemental Examiner's Answer is set forth below:

Double Patenting

Claims 1-3, 5-10 and 12-17 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13, 15-24 and 26-27 of copending Application No. 10/996,597 in view of US 6,171,586 ('586) as set forth in the non-final rejection (page 3) mailed 09/09/2008, reiterated and maintained in the final rejection (page 3) mailed 03/19/2009 and further noted in the Examiner's Answer mailed 11/19/09. Appellant's reply brief (filed 1/19/2010) was the first substantive traversal of this rejection.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to a liquid formulation of EGFR antibody, including cetuximab. 10/996,597 ('597) in claim 21 recites a concentration up to 50 mg/ml, which is highly concentrated (see claims 2-3 of the instant application). Claim 19 of '597 is drawn to making the stable antibody formulation using tangential flow filtration, which is a type of ultrafiltration (see instant specification at page 7, lines 24-25). The instant claims do not recite the inclusion of a buffer, amino acid and surfactant in the formulation.

US 6,171,586 teaches a stable aqueous pharmaceutical formulation comprising a therapeutically effective amount of an antibody not subjected to prior lyophilization, a buffer maintaining the pH in the range from about 4.5 to about 6.0, a surfactant and a polyol, along with uses for such a formulation (see Abstract). Further disclosed is that one or more other pharmaceutically acceptable carriers, excipients or stabilizers may be included in the formulation provided, such as additional buffering agents, antioxidants, and methionine (see column 23). Also disclosed is a list of buffers including citrate, acetate, histidine (an amino acid), and succinate (see column 22, lines 18-30). The polysorbate surfactants disclosed are a family of surfactants which include, polysorbate 20 (col. 22, lines 49-52). '586 also discloses sodium chloride as a tonicifier that may stabilize the antibody (see Column 22-23). Stability for at least one month at room temperature is disclosed (col. 6, lines 1-2).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare the aqueous solution disclosed in '586 to further stabilize the liquid

formulation claimed in the instant application. One would have been motivated to do so with a reasonable expectation of success by the teachings of '586 for increased stability for an aqueous preparation of an antibody suitable for therapeutic use.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Appellants argue (p. 2 middle) that the '586 patent does not teach or suggest antibody formulations comprising anti-EGFR antibodies, let alone the two specific anti-EGFR antibodies recited in the instant claims. The argument has been fully considered, but is not persuasive. The '586 patent does teach an antibody formulation comprising anti-EGFR antibodies as can be seen in the section from col. 9, line 58, through col. 10, line 63) as follows:

The invention herein relates to a stable aqueous formulation comprising an antibody. The antibody in the formulation is prepared using techniques available in the art for generating antibodies, exemplary methods of which are described in more detail in the following sections.

The antibody is directed against an antigen of interest. Preferably, the antigen is a biologically important polypeptide and administration of the antibody to a mammal suffering from a disorder can result in a therapeutic benefit in that mammal. However, antibodies directed against nonpolypeptide antigens (such as tumor-associated glycolipid antigens; see U.S. Pat. No. 5,091,178) are also contemplated....

Preferred molecular targets for antibodies encompassed by the present invention include CD proteins such as CD3, CD4, CD8, CD19, CD20 and CD34; members of the ErbB receptor family such as the EGF receptor, HER2, HER3 or HER4 receptor; cell adhesion molecules such as LFA-1, Mac1, p150,95, VLA-4, ICAM-1, VCAM and .alpha.v/.beta.3 integrin including either .alpha. or .beta. subunits thereof (e.g. anti-CD11a, anti-CD18 or anti-CD11b antibodies); growth factors such as VEGF; an interleukin such as IL8; IgE; blood group antigens; flk2/flt3 receptor; obesity (OB) receptor; mpl receptor; CTLA-4; protein C etc.

Further, the Court has held that "the test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art *presumed* to be familiar with them." *In re Rosselet*, 52 CCPA 1533, 146 USPQ 183 (CCPA 1965); emphasis in original. It was obvious to use anti-EGFR antibodies and the skilled artisan would have focused on those which were commercially available and had known or suspected therapeutic efficacy. Also, the artisan of

ordinary skill would have recognized the substitution of one known antibody for another yielding predictable results.

Appellants argue (bottom of p. 2) that the formulation of the '586 patent was "significantly more dilute compared to the antibody formulation of the instant application." (emphasis added by Appellants) The argument has been fully considered, but is not persuasive. First, claim 21 of copending application '597 specifies the anti-EGFR antibody is between 0.1mg/ml and 50 mg/ml. Second, the '586 patent teaches desired dose values from about 0.1mg/ml to about 50 mg/ml (col. 22, lines 10-14). Therefore, both '597 application and '586 patent teach using 50 mg/ml. That the copending application and patent do not claim or disclose, respectively, higher doses does not moot the obviousness of the instant invention since the claims rejected include 50 mg/ml in the claimed antibody concentration range.

Appellants argue (p. 3, first paragraph) that '597 fails to teach or suggest the concentration ranges recited in Appellants' claims and like the '586 patent, the preferred concentrations are lower than the instant claims." The argument has been fully considered, but is not persuasive. While the exact concentration range is not taught, the lower limit of the range is explicitly taught and therefore obvious. In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a *prima facie* case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990).

Appellants argue (paragraph bridging pages 3-4) that the antibodies of the '586 patent (CD18 and CD20) are not equivalent to c225 or h425 of the instant invention, but bind different epitopes such that each antibody formulation, especially for those highly concentrated, a specific method must be developed for its preparation. Also, the '586 patent teaches away from the claimed invention. The argument has been fully considered, but is not persuasive. '597 claims (e.g., claim 2) recite a formulation in which the antibody is cetuximab (aka, Mab c225) or EMD 72000 (aka, Mab h425). While the '586 patent uses anti-CD antibodies in the examples, it teaches anti-EGFR antibodies for the formulation. Therefore, it would have been obvious to use the two particular anti-EGFR antibodies disclosed and claimed in '597. The '586 patent does not teach away from using anti-EGFR antibodies, but instead provides a generally applicable method of making a stable concentrated antibody formulations. There is nothing that would have lead

the skilled artisan to expect anti-EGFR antibody formulations could not successfully be made with the disclosed method of '586 patent, particularly in view of the concentrated formulation claimed and disclosed in '597. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Appellant may file another reply brief in compliance with 37 CFR 41.41 within two months of the date of mailing of this supplemental examiner's answer. Extensions of time under 37 CFR 1.136(a) are not applicable to this two month time period. See 37 CFR 41.43(b)-(c).

For the above reasons and the reasons set forth in the Examiner's Answer, it is believed that the rejections should be sustained.

A Technology Center Director or designee has approved this supplemental examiner's answer by signing below:

/George C. Elliott, Ph.D./
Director, Technology Center 1600

/Claire Kaufman/
Examiner, Art Unit 1646